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## Diagnosis and Prognosis of Cardiac Syndrome X

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Chapter

# 9

# Summary



# SUMMARY

A significant number of patients with angina pectoris and a positive stress test for ischaemia are found to have normal coronary arteries. This combination of symptoms and (apparent) circulatory normality is called cardiac syndrome X (CSX). Patients with CSX can experience much physical and mental distress and significant restrictions to leading a normal life.

**Chapter 1** is the introduction of the thesis and gives the summary of the proposed pathophysiologic explanation for CSX. Two mechanisms that are not mutually exclusive have been proposed: myocardial ischemia that might be caused by coronary microvascular dysfunction and enhanced sensitivity to intracardiac pain or the so-called "sensitive heart" syndrome. Secondly, the problem about incidence of CSX including the various test characteristics of non-invasive stress test was described. Finally, gender differences of angina and CSX are discussed.

**Chapter 2** reviews the literature (2003-2008) on the definition and incidence of CSX, using a standardized search strategy. We included 57 articles. Nine different inclusion criteria and forty-three exclusion criteria were found in the 57 articles. When these inclusion and exclusion criteria were applied to a sample population with normal coronary angiograms, treated during one year at a general hospital, the attributable CSX incidence varied between 3% (AP, positive stress test and normal CAG) and 11% (so-called 'broad diagnosis' CSX). This variation is considerable and shows that there is a need for a generally accepted definition of CSX. Contrasting study results may be due to these different applied inclusion characteristics. An additional aspect of the review, discussed also in Chapter 8, was to assess the often-proposed gender differences of CSX occurrence.

**Chapter 3** is a case history of patient with coronary spasms. Many of these patients suffer from persistent chest pain despite optimal medical treatment, and it has been suggested that patients with coronary spasm have a disturbance in the endothelial function of their coronary arteries. We used  $^{15}\text{O}$ -labeled  $\text{H}_2\text{O}$  PET to assess myocardial perfusion and response to endothelin-receptor antagonist treatment. We measured an impaired coronary flow reserve (CFR) in 6 of 13 segments directly before the start of bosentan therapy. A repeated PET measurement after 16 weeks of bosentan treatment revealed a completely normalized CFR. Furthermore, the patient reported less frequent and less severe chest pain. Our data suggest a potential role of endothelin-receptor antagonists for patients with severe and persistent coronary vasospasms.

**Chapter 4** investigates the possible link between anxiety and ischaemia in CSX patients, whereby we obtained independent measurements of anxiety levels and the extent of ischaemia. The patients were screened with both the Trait and State Scales of the State-Trait Anxiety Inventory (STAI), and they all underwent myocardial perfusion scintigraphic imaging. Patients with a low trait anxiety had significantly less ischemic segments on the myocardial perfusion imaging than patients with a high trait anxiety ( $1.8 \pm 1.9$  vs.  $3.5 \pm 0.6$ ,  $p < 0.05$ ). For state anxiety no significant differences could be found. These results showed that CSX patients with high trait anxiety are at risk of having more extended ischemia compared to CSX patients with low trait anxiety. This suggests that anxiety-induced ischemia can occur in CSX patients, and that high trait anxiety might be a predisposing risk factor for microvascular dysfunction and/or ischaemia causing reversible perfusion defects on the SPECT imaging of CSX patients.

**Chapter 5** describes the use of first-pass perfusion cardiac magnetic resonance (CMR) to semi-quantitatively assess subendocardial and subepicardial myocardial blood flow in 20 CSX patients. As hypothesized, and already described by a single CMR study, subendocardial hypoperfusion might be present in CSX patients. In our CMR investigation a myocardial perfusion index (MPI) was calculated using the normalized upslope of myocardial signal enhancement. An index for myocardial perfusion reserve (MPRI) was calculated by dividing the MPI values at maximal vasodilatation by the values at rest. The MPI in our study population increased significantly during adenosine infusion in both the subendocardium (from  $0.091 \pm 0.020$  to  $0.143 \pm 0.030$ ;  $p < 0.001$ ) and the subepicardium (from  $0.074 \pm 0.017$  to  $0.135 \pm 0.03$ ;  $p < 0.001$ ). Both the resting and stressed states the subendocardial MPI was higher than the subepicardial MPI: respectively  $0.091 \pm 0.020$  versus  $0.074 \pm 0.017$  ( $p < 0.001$ ), and  $0.143 \pm 0.030$  versus  $0.135 \pm 0.03$  ( $p = 0.021$ ). There was a significant difference between the myocardial perfusion reserve index (MPRI) in the subendocardium,  $1.67 \pm 0.38$  and the subepicardium,  $1.98 \pm 0.64$  ( $p = 0.001$ ). The mean subendocardial: subepicardial MPRI ratio was  $0.91 \pm 0.11$ . None of the patients had a subendocardial: subepicardial MPRI ratio less than 0.72, which has been proposed as the optimal cut-off for distinguishing between normal controls and subendocardial hypoperfusion in patients with syndrome X.

We found no evidence for subendocardial hypoperfusion in patients with syndrome X. However, on our first-pass CMR images we found initial dark rim artefacts in the subendocardium in all patients. This temporary signal loss is considered to be an artefact related to the first pass sequence and is not typical for an ischaemia related defect which shows a more sustained signal loss. Our results support the idea that these artefacts have been mistaken for subendocardial hypoperfusion by Panting et al.

**Chapter 6** investigates the correlation between stress CMR and single photon emission computed tomography (SPECT) imaging, using regional flow analysis instead of global

MBF evaluation for 20 CSX patients. This investigation was to check the hypothesis that focal ischaemia occurs in relatively small myocardial regions scattered throughout the myocardium. Both the CMR and SPECT data showed in about 10% of all segments stress-induced myocardial perfusion abnormalities, which would appear to suggest focal ischaemia and patchy distributions. Of course, on the other hand, these differences might be related to possible false results of non-invasive techniques. Interestingly, the stress induced perfusion abnormalities were found in different regions of the CMR and SPECT images of the same patients. Due to the time delay between the CMR and SPECT stress tests the regional mismatch of the CMR and SPECT results, may be the result of transient focal ischaemia. We did not demonstrate a regional match of ischaemia between CMR and SPECT studies, this makes microvascular dysfunction in certain fixed coronary territories unlikely. If microvascular dysfunction is associated with ischaemia in CSX patients it may not be an irreversible pathophysiological phenomenon but rather a temporary malfunction or dysregulation. Hence, subclinical atherosclerosis may be compatible with transient focal ischaemia in CSX patients.

But if microvascular dysfunction is the case in CSX, the abnormality may not involve all coronary microvessels of a major coronary branch uniformly, but may be distributed in a patchy scattered manner. CAG only detects epicardial lesions and is unable to obtain objective evidence for this kind of myocardial ischaemia. Hence, our results could be due to the time-dependent variability of the mechanisms responsible for microvascular dysfunction, i.e. due to so-called transient ischaemia.

**Chapter 7** gives the results of cardiac PET measurements of subendocardial and subepicardial myocardial blood flow in normal healthy controls. Since PET measurements of transmural myocardial blood flow with  $^{15}\text{O}$ -labeled water are currently the gold standard, the technique can be used as a tool to assess subendocardial ischaemia in patient populations. However, only very limited data are available regarding subendocardial and subepicardial MBF measurements with  $^{15}\text{O}$ -labeled water PET, and data in normal controls are lacking. In the present study a population of 27 subjects was included without angina pectoris and a mean age of 41 years. Mean rest MBF was  $1.46 \pm 0.49$  in the subendocardium, and  $1.14 \pm 0.342 \text{ ml}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$  in the subepicardium ( $p < 0.001$ ). Stress MBF during adenosine increased to a greater extent at the subepicardial level (subendocardium vs. subepicardium:  $3.88 \pm 0.86$  vs.  $4.14 \pm 0.88 \text{ ml}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$ ,  $p = 0.013$ ). The endocardial-to-epicardial MBF ratio decreased significantly during hyperaemia ( $1.35 \pm 0.23$  to  $1.12 \pm 0.20$ ,  $p < 0.001$ ). Hyperaemic transmural MBF was inversely correlated with left ventricular end-diastolic volume index (LVEDVI) ( $r^2 = 0.41$ ,  $p = 0.0003$ ), with greater impact at the subendocardial level.

$^{15}\text{O}$ -labeled water PET enables MBF measurements with distinction of the subendocardial and subepicardial layers in the normal human heart and correlates with LVEDVI. This

PET technique may prove useful in evaluating patients with signs of ischaemia due to coronary artery disease or microvascular dysfunction.

Finally, **chapter 8** reviews the prognosis of CSX, which is generally reported as good, although a recent study reported an adverse outcome for women. Furthermore, it is stated that (pre-menopausal) women are prone to develop CSX, and some studies are focused only upon female patients. The objective of this review and meta-analysis was to evaluate the risk of a major cardiac event and the risk of persistent symptoms in different CSX patient populations. Additionally, we determined the existence and extent of the predominance of women in CSX patient populations. Sixteen studies, comprising a total of 1694 patients, met the inclusion criteria and were included in the review. With respect to CSX prognosis, it turns out that the overall major cardiac event rate for CSX patients is 1.5% per 5 years. This represents a *better* prognosis compared to the general population, suggesting that CSX patients may benefit from protective factors against coronary macrovascular disease. However, because angina pectoris in CSX is recurrent and persistent in 55% of the patients, it represents a significant impairment of the quality of life. With respect to gender, our review demonstrated that the pooled proportion of female CSX patients is 49%. This argues against the generally accepted opinion and statements that CSX occurs typically or preferentially in women.



